comprises the administration of the formulation of claim 20 to one who suffers from a sleep disorder.--

REMARKS

The Examiner is thanked for his courteous acknowledgement of the claim to priority. A certified copy of the priority application will be filed prior to the payment of the Issue Fee.

The specification has been amended to provide the section headings as suggested in 37 CFR§1.77. In addition, surplus matter relating to the identification of the inventor etc. has been deleted and, where appropriate, information relating to a summary of the invention has been placed in one section. The specification has also been revised to insert a BRIEF DESCRIPTION OF THE DRAWING. An Abstract in conformance with 37 CFR§1.72(b) is attached to this Amendment on a separate sheet of paper. The spelling errors in the specification have also been corrected by this Amendment.

Original claims 1-15 have been canceled and new claims 16-24 have been presented with the intent of avoiding each of the bases that led to the formal objections to the original claims. Claim 16 is based on the original disclosure that the formulations were controlled release formulations for use as nutritional or health food supplements as noted at page 1, lines 26-29 of the specification. Claims 17 and 20 are supported by the amounts of melatonin disclosed at page 4, lines 15-16. Claim 18 recites the preferred components as set forth in Example 1. Claim 19 specifies preferred in vitro release rates according to the method disclosed at page 9, lines 25-29 with the release values as disclosed at page 12, lines 1-5. Claim 21 points out a range of inital maximum plasma levels that are provided by the formulation of the invention as disclosed at page 6, lines 6-8. Claim 22 points out preferred in vivo release rates as disclosed at page 4, lines 1-7. Claims 23 and 24 point out the method of inducing and maintaining sleep in one suffering from a sleep disorder

by the use of preferred formulations of the invention. The new claims are believed to be in conformance with 35 U.S.C.§112, second paragraph and favorable consideration is requested.

Claims 1-7 and 9-12 were rejected as being anticipated by or in the alternative under 35 U.S.C.§103(a) as obvious over Lee et al (1999) or Lee et al. (1997).

Reconsideration of this rejection is requested in view of the newly presented claims.

Lee et al. (1999) discloses a controlled release tablet of melatonin that is made with a synthetic methacrylic/acrylic Eudragit controlled release membrane polymer which is not approved for use in nutritional food supplements. Since the term "nutritional food supplement tablet" as used in claim 16 precludes the use of a Eudragit type membrane coating, Lee et al (1999) cannot anticipate the tablet as defined by new claim 16. Claim 17 points out a tablet where the nucleus has from 1-3 mg of melatonin. Lee et al, (1999) describe a tablet weighing 52.7 +/-2.0mg which contains 1.6% of melatonin (page 73). This is equivalent to about 0.8mg of melatonin in the core of the Lee et al. (1999) tablet which does not suggest a range of 1-3mg of melatonin as pointed out in claim 17.

The concept behind the Lee et al. (1999) tablet is to provide a controlled release coating on the outer layer that provided a zero order releasing tablet. Lee et al. (1999) does not disclose or suggest the elimination of the outer release membrane coupled with the addition of an immediate release coating or cortex as pointed out in all of the newly presented claims. The zero order data of Lee et al. (1999) (page 74) may be contrasted with the in vivo data of the applicants Fig. 1 which shows the two peak blood values of melatonin when the immediate/slow release product of the invention is administered to a patient. Claims 19, 21 and 22 point out in vivo plasma levels and release rates which cannot be achieved using the Lee et al. (1999) teachings. Claims 23-24 point out the method of inducing sleep using certain formulations of the invention. Test data regarding the

efficiency of the two-peak formulations of the invention are set forth on page 15, line 8-15.

The Lee et al. (1997) Abstract does not add any disclosure to the Lee et al. (1999) publication. For these reason, it is requested that this ground of rejection not be applied against the newly presented claims.

The Bromet and Flaugh patents were applied in combination with the Lee et al. (1999) and Lee et al. (1999) references.

The Bromet patent is concerned with two layer mucoadhesive tablet that has a "loading dose layer" and a "programmed release layer". The specification at col. 4, line 7 refers to a tablet layer as a "rapid-release" layer which is defined as "an immediate flash release which may be sustained for 2 to 5 hours". A Carbopol resin is always added to the "slow release" layer of Bromet and it is understood that this product is not approved for use in foods. The in vivo blood profile of the Bromet formulation (col. 8, lines 15-25) shows that the highest concentration of melatonin is achieved at about 2 hours with a second peak at 6 hours. The data in Fig. 1 of the present application shows that the first peak is obtained at less than one hour which distinguishes the Bromet "rapid release" component from the applicant's "immediate release" component. The second peak provided by the applicant's formulation is between 2 and 3 hours while the Bromet second peak is at about 6 hours. The Bromet teachings, when considered alone or in combination, fail to suggest the applicant's immediate release concept.

The Flaugh patent is only concerned with synthetic melatonin derivatives and it fails to suggest any two component formulation. For these reasons, it is requested that the se patent not be applied to reject the newly presented claims.

An early and favorable action is earnestly solicited.

Respectfully submitted,

James V. Costigan
Reg. No. 25,669

MAILING ADDRESS:
HEDMAN & COSTIGAN, P.C.
1185 Avenue of the Americas
New York, NY 10036-2601
(212) 302-8989

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on 12/2/02

Marked Up Copy of Amendments to Specification:

Page 1, lines 1-3, rewrite the text as follows:

TITLE
CONTROLLED RELEASE MELATONIN FORMULATION [7TITLE Controlled release formulations containing am active ingredient, preferably melatonin, and the method of operation]

Page 1, line 5, delete "SUMMARY" and insert --BACKGROUND OF THE INVENTION--

Page 1, lines 15-29, delete the entire text.

Page 2, line 1, delete the entire text.

Rewrite the paragraph which begins on page 3, line 25 as follows:
--[We have found, and that is the subject of this invention,] The present invention provides new formulations for the controlled release of melatonin that are able to "mimic" the physiological [melatonin] pattern of melatonin in the peripheral blood. The new formulations are designed to initially release melatonin quickly at first and thereafter slowly and gradually. The invention provides controlled release formulations as, medicines and nutritional or health food supplements for the treatment of sleep disturbances.
BRIEF DESCRIPTION OF THE DRAWING
Figure 1 is a graphical depiction of the plasma profile and the saliva profile obtained in vivo by the administration of a formulation of the invention containing 1 mg of melatonin in the cortex coating and 2mg of melatonin in the nucleus of the tablet.--

Page 4, line 1, insert: DETAILED DESCRIPTION OF THE INVENTION

Rewrite the paragraph that begins on page 8, line 7 as

follows:

--A non-limiting example of the unit formulation for the formation of the nucleus [nucleuss] is:

granulate (from above)	68mg
hydroxypropylmethylcellulose	31mg
lactose	75mg
aerosil 200	0.35mg
Mg stearate	1.65mg--

Rewrite the paragraph that begins on page 8, line 17 as follows:

--A nonrestrictive example of the formulation in solution for the "cortex" is:

melatonin	2.7%
hydroxypropylmethylcellulose	8.8%
lactose	6.4%
titanium dioxide [bioxide]	0.8%
ethyl alcohol	17.3%
purified water	64%--